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EXAMINER	
HUYNH, CARLIC K	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,931	HUI ET AL.	
	Examiner	Art Unit	
	CARLIC K. HUYNH	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45 and 47-86* is/are pending in the application.

4a) Of the above claim(s) *85 and 86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45 and 47-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of applicants' amendments and remarks filed on November 21, 2007 is acknowledged.

Status of the Claims

1. Claims 45 and 47-86 are pending in the application in response to the Non-Final Rejection filed on July 11, 2007. It is noted Applicants previously cancelled claim 46 in an "Amendment- After Non-Final Rejection" filed on July 11, 2007. Claims 85-86 were previously withdrawn in the reply to a "Restriction/Election" filed on November 20, 2006. Accordingly, claims 45 and 47-84 are being examined on the merits herein.

The rejections made under 35 U.S.C. 102(e) have been withdrawn in view of Applicants' amendments.

The following new grounds of rejections are necessitated by Applicants' amendments.

Specification

2. The use of the trademark Filamatic® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 45 and 47-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg et al. (US 5,677,472 as cited in the IDS) in view of Fisher et al. (US 5,840,661), Unger et al. (US 5,585,112), and Unger (US 6,416,740), and as evidenced by Senior et al. ((Biochimica et Biophysica Acta, 1991, 1062, pp. 77-82).

Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in an organic solvent mixture of polar organic solvent (e.g. methanol) and

essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13^{O}-25^{O} C, and drying the precipitate (see example 1, 2, 6, and claim 1). The concentration of sphingomyelins in the solvent is 2-20 mg/ml (column 6, lines 44-48). Nyberg et al. specifically indicate separation of phospholipids into different phases (column 5, lines 53-57; example 1, lines 56-67; and example 2).

Regarding claim 50, Nyberg et al. teach warming the non-aqueous solvent system to 25^{O} C, which meets the limitations of the instant claim (example 1).

Nyberg et al. explicitly indicate similar methods of extracting a phospholipid utilizing suitable solvent systems (column 3, lines 6-15). Nyberg et al. further teach the precipitation of a phospholipid mixture, "brown phase," by using suitable solvent systems (examples 2-3; specifically column 9, lines 54-57). Nyberg et al. also acknowledge the wide use of phospholipids in medical field (column 1, lines 17-30).

Nyberg et al. do not employ methyl t-butyl ether as an intermediate solvent and further fails to prepare phospholipid suspensions.

The teachings of Fisher et al. are solely used to show that methyl t-butyl ether and acetone are art equivalent solvents (column 59, lines 55-60).

Unger et al. teach suitable mixtures of phospholipids including dipalmitoylglycerophosphatidylcholine, dipalmitoylglycero phosphatidic acid, and phosphatidylethanolamine-PEG 5000 in combination with a gaseous perfluorobutane. Unger et al. further use polyols, such as polyethylene glycols, in preparing phospholipid suspensions (abstract; columns 2, 10, 12, 22, 25; and examples 1-3).

Unger teaches a method for sterilizing phospholipids suspensions (column 52, lines 47-56).

As evidenced by Senior et al., Senior et al. disclose dipalmitoylphosphotidylethanolamine (DPPE) covalently may be coupled to methoxypolyethylene glycol (MPEG 5000) (abstract). Senior et al. further disclose poly(ethylene glycol) (PEG) and MPEG 5000 are known in the art as equivalent substances to alter the surface properties of liposomes (page 78).

Accordingly, absence the showing of unexpected results, it would have been obvious to one of ordinary skill in the art to substitute the acetone of Nyberg et al. with methyl t-butyl ether, because as shown by Fisher et al., such organic solvents are art equivalents.

Further, absence the showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the phospholipid blend of Nyberg et al., as modified by Fisher et al., in polyols such as polyethylene glycol as taught by Unger et al., and formulate suitable phospholipid suspensions for therapeutic use, because such suspensions, as recognized by Nyberg et al. and taught by Unger et al., are readily used in the arts of drug delivery and ultrasonic imaging applications.

The motivation to combine the acetone as taught by Nyberg et al. with the methyl t-butyl ether as taught by Fischer et al. is acetone and methyl t-butyl ether are art equivalent organic solvents.

The motivation to combine the phospholipid blend of Nyberg et al. with the phospholipid blend of Fischer et al., Unger et al., and Unger is they are suitable phospholipid suspensions for use in medical imaging such as ultrasonic imaging applications.

Regarding claim 45, Nyberg et al. teach the concentration of sphingomyelin in a solvent to be 2-20 mg/ml (column 6, lines 44-48), which meets the limitations of the instant claims. It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the concentration of the phospholipids in a solvent provided in a composition, according to the guidance set forth in Nyberg et al., to provide a composition having the desired concentration of phospholipid in a solvent. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 56-57, Unger et al. teach providing a dispersed phospholipids blend solution at 50^{O}C, which meets the limitations of the instant claims (example 4A).

Regarding claims 58-59, Unger et al. teach the ratio of solid phospholipids blend to polyol solvent is 5 mg/mL, which meets the limitations of the instant claims (example 1). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the ratio of solid phospholipids blend to polyol solvent provided in a composition, according to the guidance set forth in Unger et al., to provide a composition having the desired ratio of solid phospholipids blend to polyol solvent. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 68-70, Unger teach lipid aggregates are 200 nm in size and may be as small as 5-10 nm in size, which meets the limitations of the instant claims (column 26, lines 22-23).

Regarding claims 71-72, Nyberg et al. teach heating the aqueous solution to 40^{O}C (example 5). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the aqueous solution temperature provided in a composition, according to the guidance set forth in Nyberg et al., to provide a composition having the desired aqueous solution temperature. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 73-74, Unger et al. teach the phase transition temperature is 41^{O}C and the lipid solution temperature is 42-50^{O}C, which meets the limitations of the instant claims (example 8). It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the lipid solution temperature provided in a composition, according to the guidance set forth in Unger et al., to provide a composition having the desired lipid solution temperature. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Regarding claims 75-78, Unger teaches filtering a phospholipid suspension through a sterilizing filter (column 52, lines 38-41), filtering using at least 1 filter (column 52, lines 4 and

17-19), the temperature of the filter (column 52, lines 57-59), and the filter pore size of 0.1-5 μm (column 52, lines 38-39), which meet the limitations of the instant claims.

Regarding claims 79-82, Unger teaches dispensing the phospholipid suspension into a vial (column 52, lines 26-29), a perfluorocarbon gas (column 28, line 21), perfluoropropane (column 28, line 26), and the method to exchange gas (column 29, lines 15-16), which meet the limitations of the instant claims.

Regarding claims 83-84, Unger teaches a method of sterilization (column 52, lines 26-29 and 47-56).

Response to Arguments

4. Applicant's arguments, see "Remarks" filed on November 21, 2007, with respect to "Rejections under 35 U.S.C. § 103" to claims 45 and 47-84 has been fully considered and are not persuasive. The Applicants argue that Nyberg et al. disclose far greater relative amounts of sphingomyelin than either PE or PC, after precipitation, than was contained in the starting solution. Applicants further argue that Nyberg et al., Fisher et al., Unger et al, and Senior et al. fail to teach preserving the phospholipids in the final precipitate.

Examiner responds that Nyberg et al. teach the concentration of sphingomyelins in solvent to be in the range of 2-20 mg/ml (column 6, lines 44-48). Nyberg et al. further teach purifying the sphingomyelin product (see column 6, lines 35-40). Thus, the Rejections under 35 U.S.C. § 103 to claims 45 and 47-84 are maintained.

5. Claims 45 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. (US 6,521,211).

Unger et al. teach a process for preparing phospholipids comprising 6% DPPA, 40% DPPE-PEG5000, and 54% DPPC (column 135, lines 29-31). The phospholipid mixture is added to a non-aqueous solvent system of methanol and toluene (column 135, line 34). The mixture was warmed to 55^{O}C and allowed to form a thick gel (column 135, lines 36 and 39). Methyl t-butyl ether was added to the mixture to precipitate the solid material at 25^{O}C and placed in a vacuum oven to dry (column 135, lines 40-42 and 44).

It is noted that Unger et al. teach preparing phospholipids comprising DPPA, DPPE-PEG5000, and DPPC minus the weight of DPGS-PEG-KQAGDV (column 135, 29-30). It would be obvious to one skilled in the art that the phospholipids of Unger et al. contain DPPA, DPPE-PEG5000, and DPPC.

Regarding claim 45, Unger et al. teach a process for preparing phospholipids comprising 6% DPPA, 40% DPPE-PEG5000, and 54% DPPC, which were then mixed in a solvent system of methanol and toluene (column 135, lines 29-31 and 34), which meets the limitations of the instant claims. It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the concentration of DPPA, DPPE-PEG5000, and DPPC in a solvent system of methanol and toluene provided in a composition, according to the guidance set forth in Unger et al., to provide a composition having the desired concentration of about 5 to about 15 mg/mL of lipid blend in a solvent. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the

optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Response to Arguments

6. Applicant's arguments, see "Remarks" filed on November 21, 2007, with respect to "Rejections under 35 U.S.C. § 103" to claims 45 and 47-52 has been fully considered and are not persuasive. The Applicants have argued that Unger et al. do not utilize a relative ratio of lipids to solvent of about 5:1 to 15:1.

In response, Examiner argues Unger et al. teach a process for preparing phospholipids comprising 6% DPPA, 40% DPPE-PEG5000, and 54% DPPC (column 135, lines 29-31). The phospholipid mixture is added to a non-aqueous solvent system of methanol and toluene (column 135, line 34). It would be obvious that the skilled artisan can add enough of the non-aqueous solvent system of methanol and toluene to yield a relative ratio of lipids to solvent of about 5:1 to 15:1. Thus, the Rejections under 35 U.S.C. § 103 to claims 45 and 47-52 are maintained.

Conclusion

7. No claims are allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

ckh